**INTRODUCTION**

Influenza, a highly contagious, airborne respiratory tract infection, is responsible for approximately 36,000 deaths and more than 200,000 hospitalizations in the U.S. every year.\(^1\)\(^-\)\(^3\) It causes illness in about 10% to 20% of the general population annually,\(^1\)\(^,\)\(^4\) resulting in substantial losses in work, productivity, and an estimated $3 to $15 billion in health care costs.\(^1\)\(^,\)\(^5\)

Rates of infection are highest among children five to 14 years of age, but rates of serious illness and death are highest among children younger than two years of age, persons 65 years of age and older, and persons of any age with medical conditions, such as cardiovascular and pulmonary diseases. People in these groups and with these illnesses are at an increased risk of complications.\(^1\)\(^,\)\(^6\)\(^-\)\(^8\)

Although complete protection might not be provided to all susceptible individuals, the single most effective method of preventing influenza, its complications, and death is immunoprophylaxis with vaccination.\(^1\)\(^,\)\(^5\)\(^-\)\(^8\) Each year, global surveillance of influenza aids in the identification of antigenic variations, allowing for annual standardization of the influenza vaccines.\(^6\)\(^,\)\(^8\) The vaccines are also formulated to consist of two types of influenza A strains and one type of influenza B strain, according to U.S. Public Health Service (USPHS) recommendations and requirements.\(^8\)

To receive optimal protection from influenza infection during the peak months of December through March, individuals should receive vaccinations during October and November.\(^6\)

Currently, two types of vaccine are available in the U.S. (Table 1):\(^9\)\(^,\)\(^10\)

- live, attenuated influenza vaccine: FluMist (MedImmune/Wyeth)
- trivalent, inactivated influenza vaccine: Fluzone (Sanofi Pasteur); Fluvirin (Chiron); and Fluarix (GlaxoSmithKline).

Fluarix is an intramuscularly administered vaccine, indicated for patients 18 years of age or older against influenza virus types A and B, which are contained in the vaccine. It is the newest of the trivalent, inactivated, split-virion influenza vaccines. Fluarix was approved on August 31, 2005, and became available for use during the 2005–2006 influenza season.\(^8\)\(^-\)\(^10\)

**PHARMACOLOGY AND PHARMACOKINETICS**

Fluarix consists of the hemagglutinins of three virus strains expected to be circulating during the upcoming winter season. Three strains were included in the 2005–2006 vaccine formulation:

- A/New York/55/2004 (H3N2) (an A/California/7/2004-like strain)
- A/New Caledonia/20/99 (H1N1)
- B/Jiangsu/10/2003 (a B/Shanghai/361/2002-like strain)

Although the vaccine is formulated without preservatives, thimerosal is used during the early stages of manufacturing. It is removed by subsequent purification techniques (to less than 1.25 mcg of mercury per dose).\(^6\)\(^,\)\(^8\)

Influenza vaccination typically provides protection from influenza within...
two weeks of administration. An annual vaccine protects 70% to 90% of healthy adults from contracting illness. It also allows milder cases of illness to develop in those who receive the vaccine, compared with those who do not, and it is about 80% effective in preventing death among the elderly.6,8,11

**CLINICAL TRIALS: IMMUNOGENICITY IN ADULTS**

In Study FLUARIX-US-001, a randomized, double-blind, placebo-controlled trial, researchers evaluated the immune responses of 745 healthy adults, 18 to 64 years of age, to each of the antigens contained in Fluarix vaccine. Three influenza strains were contained in the vaccine:

- A/New Caledonia/20/99 (H1N1)
- A/Wyoming/3/2003 (H3N2)
- B/Jiangsu/10/2003

Serum obtained from each study participant 21 days after vaccination was compared with the sera of 190 subjects who received a placebo vaccine of normal saline solution.8,11 The purpose of this study was to determine the hemagglutinin–inhibition (HI) antibody titers and seroconversion rates at 21 days after the administration of the vaccine. The criteria for these titers were set at 1:40 or higher after vaccination, a figure that has been associated with at least 50% protection against infection.

At 21 days after vaccination, the Fluarix patients exceeded the HI minimum immunogenicity rate of 87.5% for each antigen and the seroconversion minimum immunogenicity rate of 55.4% for each antigen (Tables 2 and 3).11

**ADVERSE DRUG REACTIONS**

Prior to the approval and marketing of Fluarix, the vaccine was administered to 1,271 adults in clinical trials. In Study FLUARIX-US-001, a total of 952 healthy adults, 18 to 64 years of age (54% female and 80% Caucasian), were assessed for adverse drug events (ADEs) after the administration of Fluarix or placebo. Solicited ADEs were observed and collected on the day of vaccination and on the three subsequent days (Table 4). Unsolicited events that occurred within 21 days of vaccination were also recorded on diary cards, and medical histories were disclosed by the study subjects.

The unsolicited ADEs associated with Fluarix, compared with placebo, respectively, included upper respiratory tract infection (3.9% vs. 2.6%), nasopharyngitis (2.5% vs. 1.6%), nasal congestion (2.2% vs. 2.1%), diarrhea (1.6% vs. 0%), influenza-like illness (1.6% vs. 0.5%), vomiting (1.4% vs. 0%), and dysmenorrhea (1.3% vs. 1.0%). The subjects reported that most ADEs were mild and self-limiting.8,11

**CONTRAINDICATIONS**

Fluarix is prepared from influenza viruses propagated in embryonated chicken eggs and therefore should not be administered to individuals with any known systemic hypersensitivities to egg proteins (i.e., eggs or egg products) or chicken proteins. People with known hypersensitivities to any component of Fluarix or those who have had a life-threatening reaction to the previous administration of any influenza vaccine should not receive the vaccine.

Vaccination should be also delayed in persons with active neurological disorders.8

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**Table 2** Hemagglutinin–Inhibition Antibody Titers of 1:40 or Higher in Study FLUARIX-US-001

<table>
<thead>
<tr>
<th>Influenza Strain (Antigen)</th>
<th>Placebo (N = 190)*</th>
<th>Fluarix (N = 745)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-vaccination</td>
<td>21 Days after Vaccination</td>
</tr>
<tr>
<td>A/New Caledonia/20/99 (H1N1)</td>
<td>52.1 (44.8–59.4)</td>
<td>51.1 (43.7–58.4)</td>
</tr>
<tr>
<td>A/Wyoming/3/2003 (H3N2)</td>
<td>65.3 (58.0–72.0)</td>
<td>65.3 (58.0–72.0)</td>
</tr>
<tr>
<td>B/Jiangsu/10/2003</td>
<td>48.9 (41.6–56.3)</td>
<td>51.1 (43.7–58.4)</td>
</tr>
</tbody>
</table>

* Percent of patients with hemagglutinin–inhibition titers of 1:40 or higher (95% confidence interval).

**Table 3** Seroconversion in Study FLUARIX-US-001

<table>
<thead>
<tr>
<th>Influenza Strain (Antigen)</th>
<th>Placebo (N = 190)*</th>
<th>Fluarix (N = 745)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21 Days after Vaccination</td>
<td>21 Days after Vaccination</td>
</tr>
<tr>
<td>A/New Caledonia/20/99 (H1N1)</td>
<td>0 (0.0–1.9)</td>
<td>59.6 (56.0–663.1)</td>
</tr>
<tr>
<td>A/Wyoming/3/2003 (H3N2)</td>
<td>1.1 (0.1–3.8)</td>
<td>61.9 (58.3–65.4)</td>
</tr>
<tr>
<td>B/Jiangsu/10/2003</td>
<td>1.1 (0.1–3.8)</td>
<td>77.6 (74.4–80.5)</td>
</tr>
</tbody>
</table>

* Percent of patients with at least a four-fold rise in hemagglutinin–inhibition titers of 1:40 or higher (95% confidence interval).
Fluarix should not be administered in persons with bleeding disorders (i.e. hemophilia, thrombocytopenia), patients receiving anticoagulant therapy, or persons in whom Guillain-Barré syndrome has occurred within six weeks of prior influenza vaccination unless the potential benefit outweighs the risk of vaccination.

The tip cap and rubber plunger of the prefilled syringes contain dry, natural latex rubber, which may potentiate an allergic reaction in people with latex sensitivities. Therefore, epinephrine injection (1:1,000) and other agents used in the control of immediate allergic reactions must be readily available in the control of immediate allergic reaction following the administration of Fluarix.

Fluarix is a pregnancy category C agent. It is not known whether this vaccine causes fetal harm when administered to pregnant women or whether it affects reproduction capacity. It is also unknown whether Fluarix is excreted in human milk; therefore, nursing women should exercise careful consideration and caution with this drug.8

### DOSAGE AND ADMINISTRATION

Fluarix is available as a colorless to slightly opalescent suspension in prefilled syringes containing single 0.5-ml doses. The syringes should be kept in their original packaging, protected from light, and should be stored in the refrigerator between 2°C and 8°C (36°F and 46°F) without freezing. Each 0.5-ml prefilled syringe should be shaken well and inspected for any particulate material or discoloration prior to administration. Fluarix should be injected intra-muscularly, preferably in the deltoid muscle region of the arm. The vaccine should not be injected in the gluteal area or areas where a major nerve trunk may exist.8

### CONCLUSION

Disruptions in the manufacturing or delays in the distribution of influenza vaccines have occurred during three of the last five influenza seasons in the U.S.10,14 In October 2004, the Chiron Corporation notified the U.S. Centers for Disease Control and Prevention (CDC) that none of its influenza vaccine (Fluvirin) would be available for distribution during the 2004–2005 influenza season, thereby reducing the anticipated supply of trivalent inactivated vaccine by approximately 50% in the U.S. In response to this urgent situation, the CDC, in coordination with its Advisory Committee for Immunization Practices (ACIP), issued interim recommendations for influenza vaccinations to ensure appropriate prioritization of vaccine administration to those at greatest risk of infection, complications, and death.10,14,15

To prevent future shortages of influenza vaccines, steps to ensure adequate supply are necessary. One step was the approval of Fluarix influenza virus vaccine using the accelerated approval process of the Food and Drug Administration (FDA). This process allows products that treat serious or life-threatening illnesses to be approved based on successfully achieving an endpoint that is reasonably likely to predict ultimate clinical benefit.

Fluarix is the first vaccine to be approved by this accelerated process. As a result, its manufacturer (GlaxoSmithKline) will continue to conduct clinical studies to assess and verify the benefits of the vaccine.15

### REFERENCES


| Table 4 Solicited Adverse Events in Study FLUARIX-US-001 |
|----------------------------------|-----------------|-----------------|
| **Adverse Drug Event**  | **Placebo (N = 192)*** | **Fluarix (N = 760)*** |
| Pain | 12.0 (7.7–17.4) | 54.7 (51.1–58.3) |
| Redness | 10.4 (6.5–15.6) | 17.5 (14.9–20.4) |
| Swelling | 5.7 (2.9–10.0) | 9.3 (7.4–11.6) |
| Muscle aches | 12.0 (7.7–17.4) | 23.0 (20.1–26.2) |
| Fatigue | 17.7 (12.6–23.9) | 19.7 (17.0–22.7) |
| Headache | 21.4 (15.8–27.8) | 19.3 (16.6–22.3) |
| Arthralgia | 6.3 (3.3–10.7) | 6.4 (4.8–8.4) |
| Shivering | 2.6 (0.9–6.0) | 3.3 (2.1–4.8) |
| Fever ≥100.4°F | 1.6 (0.3–4.5) | 1.7 (0.9–2.9) |

*Percent of patients with solicited adverse events within four days of vaccination (95% confidence interval).